

## REMARKS

### Introduction

Responsive to the communication mailed November 4, 1999, Applicants provide the following remarks.

The claims have been carefully reviewed in light of the rejections in the Office Action. Claims 36, 37, 45, 46, 54, 55 and 60 have been canceled. In order to more distinctly claim the features which achieve the advantages of the invention, claims 33, 34, 38, 39, 42, 43, 47, 48, 49, 51, 52, 56, 59 and 60 have been amended. Claims 61, 62, and 63 have been added. No new matter has been added by this amendment. Reconsideration and reexamination of the application in view of the above amendments and the following remarks is requested.

### Applicant's Invention

Prior to responding to the rejections in the most recent Office Action, a brief narrative directed to the nature and advantages of the present invention appears desirable. The present invention is generally a method of delivering a substance, L-Arginine or its derivatives, which are nitric oxide precursors,

into tissue. More specifically, the invention comprises a method of moving the substance from a delivery vehicle into tissue by creating a hostile biophysical environment which causes the substance to migrate from the delivery vehicle to the skin where it is absorbed by tissue. In an alternative embodiment, the substance can be packaged , eg., in a liposome, said liposome being at a concentration sufficient to create a hostile biophysical environment which causes the liposome to migrate from the delivery vehicle to the skin where the substance is released from the liposome and absorbed by the tissue.

Applicant has discovered that the administration of L-arginine, in its various forms, using the method of the present invention, to superficial ulcers causes healing of the ulcers ; administration to the scalp causes hair growth; administration to the penis enhances erectile function.

It is believed that the present invention, as described in the Application with the claims amended and submitted herewith, is directed to a great advance in the art. Problems of the prior art in delivering an effective amount of L-arginine into tissue in order to bring about such remarkable, unexpected and unobvious results have been solved by the method of the present invention. No other reference or combination of references to date has led to these

results. No other reference, alone or in combination, suggests the design and use of a hostile biophysical environment for drug delivery into tissue.

Although it is true that there are some similarities between Applicant's invention and the cited references, there are unexpected properties in Applicant's invention, to wit, a quantum leap forward in the level of results achieved by the method of using a hostile biophysical environment. The significant difference in results suggests that Applicant has discovered a new and very useful improvement. The improvement is due to a significant difference in the method over previous methods, for which Applicant respectfully submits, he should be entitled to his claims, as amended.

### **The Rejections**

#### **Rejections Under 35 U.S.C. § 112**

On page 2 and page 4 of the Office Action the Examiner has rejected claims 39-41, 47-50, and 56-58 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that "It is not clear whether or not the materials in claims 39 and 47, etc. are meant to be used as alternatives or in combination since this is not stated in the claim." Applicant agrees with the Examiner that it was not clear from

the original claims whether or not the materials therein are meant to be used as alternatives or in combination. In response to these rejections, claims 39, 47 and 56 have been amended to insert the word “and” between the last two substances in the list of materials which comprise the delivery vehicle, in order to correct the typographical error in the original claim. It is believed that this amendment removes the basis of the Section 112 rejection for these claims as well as for claims 40, 41, 48, 49, 50, 57 and 58, each of which is dependent on one of the amended claims, 39, 47, 56.

In addition, spelling errors in claims 39, 47, and 56 were corrected.

#### **Rejections Under 35 U.S.C. §102 and §103**

On pages 2 and 3 of the Office Action, the Examiner has rejected claims 33-34, 38, 39, 51-54, 56, 59 and 60 under 35 U.S.C. § 102(a) as anticipated by or, in the alternative, under U.S.C. § 103 (a) as obvious over Weuffen et al. (USP 5,629,002.

#### **The Weuffen Reference**

On page 4, last paragraph, the Examiner states that “...the fact that the Weuffen reference does not explicitly disclose that arginine is the active ingredient is immaterial.” The Examiner continues, “In any case it is not

clear what the L-arginine is doing in Weuffen's composition if it does not penetrate the skin." The Examiner continues, on page 5, "each and every element of applicant's claims is therefore present although not necessarily explicitly disclosed."

On page 9, last paragraph, the Examiner refers to the Applicant's earlier argument that the "mere fact that Hechtman and Weuffen disclose arginine and salt in no way implies that an hostile biophysical environment is inherently present." The Examiner continues, "[F]irstly, the phrase 'hostile biophysical environment' is not present in the claims." The Examiner states further that "there is nothing in the claims about an hostile biophysical environment." On page 10, still in regard to Hechtman and Weuffen, the Examiner states that "[I]n any case it is applicant's burden to prove that the concentration of salts in the reference is not high enough to cause absorption."

First, in response to these rejections, the Applicant has cancelled claims 36, 37, 45, 46, 54, 55 and 60, and has amended all remaining claims to recite the fact that a delivery vehicle for the substance, L-arginine and its derivatives, contains a concentration of ionic salt sufficient to create an "hostile biophysical environment" which causes the substance to migrate from the vehicle to the skin where the substance is absorbed by tissue.

Support for these amendments is found throughout the specification, in particular at pages 3 (first, second and third paragraphs), page 4, second paragraph, "...the agent which creates the hostile biophysical environment is sodium choride at a concentration sufficient to aid in tissue absorption." Further support is found at page 5, first paragraph, page 6, last paragraph, continued on page 7.

In addition, claims 61, 62, and 63 have been added in order to better describe the subject matter that Applicant believes is his invention. In the added claims, the delivery vehicle contains the L-arginine or its derivatives within a liposome, "said liposome being at a concentration sufficient to create an hostile biophysical environment which causes the liposome to migrate from the delivery vehicle to the skin where the substance is released from the liposome and absorbed by the tissue." Support for the added claims is found in the specification at pages 6 , last paragraph, and 7. On page 7, first paragraph (continued from page 6) a "highly hydrophobic environment" created by "decreasing water content and increasing lipid, oil and/or wax content" is stated as an example of a "biophysically hostile environment." Those skilled in the art know that a liposome is an example of a highly hydrophobic environment. Further, on page 7, first paragraph, liposomes are

given as one of the “[E]xamples of packaging which would be carried into tissue.”

All of Applicant’s claims are now limited to an “hostile biophysical environment.”

Second, in response to the rejections based on Weuffen, Applicant submits that there is no hostile biophysical environment in any example in the Weuffen reference. Even in Example 10, which may be the closest to Applicant’s invention, the ionic strength of the ions sodium, potassium, magnesium, and chloride is less than that of blood. Further, even all the ionic components of Example 10 taken together add up to a lower ionic strength than that of blood. There is no construction that can be made of the Weuffen reference that would constitute “an hostile biophysical environment.” In addition, the solution of the reference contains 25 g/L sorbitol and 25 g/L xylitol. Both individually, and the two additively would draw molecules like L-arginine out of the tissue rather than aid in getting them across the skin into the cells and fluid of the scalp. Not only is there no hostile biophysical environment in Weuffen, but his solutions would tend to remove, rather than add L-arginine to the tissue. Weuffen does seem to grow hair, but, based on the foregoing analysis, it could not be by the method of the Applicant’s invention.

Based on the above amendments and the foregoing remarks, Applicant respectfully requests that the rejections based on the Weuffen reference be withdrawn.

**The Hechtman Reference**

On page 3 of the Office Action, the Examiner has rejected claims 33-34 and 39 under 35 U.S.C. § 102(a) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Hechtman (USP 5,595,753).

In response to these rejections, as with Weuffen, Applicant points out that he has cancelled claims 36, 37, 45, 46, 54 and 55, and has amended all remaining claims to recite the fact that a delivery vehicle for the substance, L-arginine and its derivatives, contains a concentration of ionic salt sufficient to create an “hostile biophysical environment” which causes the substance to migrate from the vehicle to the skin where the substance is absorbed by tissue.

Further, in the added claims, 61, 62, and 63, the delivery vehicle contains the L-arginine or its derivatives within a liposome, “said liposome being at a concentration sufficient to create an hostile biophysical environment which

causes the liposome to migrate from the delivery vehicle to the skin where the substance is released from the liposome and absorbed by the tissue.”

All of Applicant’s claims are now limited to a “biophysically hostile environment.” The above amendments should be fully responsive to the Examiner’s reasoning, on page 5, last paragraph. The Examiner there states that although the electrolyte in Hechtman is not limited to an ionic strength which is high enough to create an hostile biophysical environment, the term ‘hostile biophysical environment’ does not appear in Applicant’s claims.

The Examiner continues, on page 5, that, as with Weuffen, “it does not appear reasonable that the arginine of patentees is not absorbed.” Again, the Examiner states that “it is applicant’s burden to show that applicant’s property or function is not present in the reference above.

In response to the remarks by the Examiner regarding the Hechtman reference, Applicant respectfully points out that the Hechtman patent speaks for itself. First, Hechtman has nothing that is even close to a hostile biophysical environment. Applicant’s claims are now all limited to a hostile physical environment.

Second, although L-arginine is used by Hechtman, it is not clear that it actually does anything because there is no dose response for L-arginine. In Fig. 1, all doses are equally effective within any kind of experimental error. It is possible that just applying KY jelly with a little rubbing would achieve the same results. The results cannot be caused by the L-arginine.

Similarly, in Fig. 2, although there is no figure legend to identify symbols, it appears that saline (open circles) produces the greatest effect, while the inhibitor of L-arginine, L-NAME works similarly to L-arginine, ie., less well than saline.

Finally, in Fig. 3, 1 mg of L-arginine actually works better than a larger amount, 10 mg of L-arginine. L-NAME does block L-arginine here, as it should. However, at all except the last time point the results with and without inhibitor are equivalent unless the n is very high.

In summary, there is no hostile biophysical environment and there is little or no evidence that L-arginine is doing anything in the Hechtman reference. Indeed, saline seems to work the best.

Accordingly, based on the above amendments and the foregoing remarks, Applicant respectfully requests that the rejections based on the Hechtman reference be withdrawn.

**The Rejections Based on a Combination of References Under 35 U.S.C. § 103(a)**

On page 3, claims 33-60 have been rejected by the Examiner under 35 U.S.C. § 103 (a) as being unpatentable over Garfield in view of Hechtman, Altadonna (USP 5,853,768), Cooke (USP 5,428,070), Saavedra (USP 5,632,981) and Cooper.

In response to these rejections, Applicants agree with the Examiner (page 9 of the Office Action) that a “piecemeal analysis” of the rejections referenced in the preceding paragraph is not appropriate. Applicants also point out that the claims have been amended to limit the invention to a “hostile biophysical environment.”

However, before one can begin an analysis of the rejections, it must be noted that the “references” cited against Applicant’s application must, in fact, be references. The only relevant “references” are those which disclose some feature of Applicant’s invention. Based on the above analysis of the

Hechtman reference, and in light of the foregoing amendments, it is clear that Hechtman does not disclose any features of the Applicant's invention, as now claimed. Therefore, it is not a valid reference.

Garfield, Cooke, and Saavedra do teach the use of a nitric-oxide precursor.

Altadonna teaches that iodide salts enhance penetration of pain relief components of a particular composition. Cooper teaches the use of ionic surfactants (salts) to increase penetration of polar materials. However, neither Altadonna nor Cooper teaches the creation of an hostile biophysical environment as claimed, to drive L-arginine from a delivery vehicle to the skin where it is absorbed by the tissue.

Having set forth the features of interest in the references, Applicant now proceeds to analyze the rejections made under this combination of references. A valid analysis of a rejection based on a combination of references must be "two-part."

First, there is no suggestion in the prior art represented by the above references that they be combined in the manner proposed by the Examiner to yield a hostile biophysical environment.

Second, even if it is determined that there is a suggestion in the prior art to combine the above references in the manner proposed by the Examiner, Applicant points out that the structure of the method that results from the Examiner's proposed combination of references would not meet the terms of Applicant's proposed amendments to the claims, namely, the creation of an hostile biophysical environment. This is because the feature set forth in the amendments, that is, the creation of an hostile biophysical environment, is not found in any of the references separately, and such feature would therefore be lacking in any combination of the references.

None of the references, either singly or in combination even approach a hostile biophysical environment which comprises the subject matter of Applicant's invention. There is no teaching or suggestion in any of the references, either singly or in combination, to use a concentration gradient of such magnitude that would constitute a hostile biophysical environment. But for such an hostile biophysical environment , the effects described in Applicant's specification would not be produced. The effects of Applicant's invention are an unexpected and surprising result. The causal connection between an hostile biophysical environment and its effect is not so obvious that the perception of the connection did not involve a discovery which will support a patent.

Accordingly, Applicant submits that the independent and dependent claims, as amended, and the new claims submitted herein, are patentable over the prior art, because each contains limitations which would not be known or obvious over the prior art, for the reasons provided above.

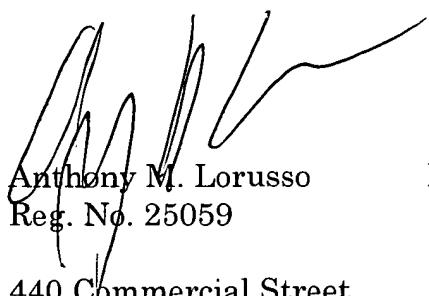
It is believed that there are no fees are currently due. In the event of any inadvertent fee deficiency, authorization is hereby granted to charge such deficiency to deposit account 12-2147.

### Conclusion

All of the stated grounds of rejection have been properly met or traversed. The claims, as amended, are not obvious in view of the above-mentioned prior art. Therefore, it is submitted that this application is in condition for allowance, and reconsideration and allowance thereof are respectfully requested.

Respectfully submitted,

LORUSSO & LOUD

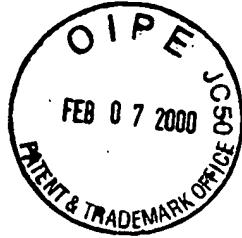


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Jacqueline M. Arendt